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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/634,960	08/08/2000	Frank Karlsen	5775.018	3988

30589 7590 03/28/2002

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 03/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/634,960	Applicant(s) Karlsen
	Examiner Jehanne Souaya	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 11, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 6-8, and ~~14-19~~ 13-19* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 6-8, and ~~14-19~~ 13-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____. is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4,5,8*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Please note the art unit designation for the examiner has changed from 1655 to 1634.

Election/Restriction

1. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged.

Priority

2. Applicant's claim for priority under 35 USC 119(e) to provisional application 60/149,365, filed August 13, 1999, is noted. Primers with SEQ ID NOS 1 and 14 were disclosed in the provisional application, however primers with SEQ ID NOS 2-3 and 15-16 were not. Therefore, claims 7 and 13 and primers 1 and 14 have been awarded the benefit of the earlier filing date. Applicant should amend the claims such that each claim receives the benefit of the same filing date.

Specification

3. The use of the trademark PicoGreen™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Sequence Listing

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6-8, and 14-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 6 is indefinite because the claim fails to include a positive process step relating back to the preamble. The preamble states a method of detecting microorganisms in a liquid or liquefied sample but the final process step is treating the DNA sample under PCR conditions. Therefore the method is unclear as to whether it is to detecting microorganisms or to treating a DNA sample under PCR conditions.

B) Claim 8 is indefinite as a positive process, detection step is not present in claim 6, the last positive process step in claim 6 is "treating a DNA sample under PCR conditions...",

therefore it is unclear which part of the method of claim 6 is being referred to. Claim 8 should also be amended to recite " *the* presence of ..." in line 2.

C) Claim 14 is indefinite as the phrase "corresponding oligonucleotide primer of claim 3" in unclear. The term "corresponding" does not make clear the relationship between the second primer of claim 14 and the oligonucleotide primer of claim 3 as it is not understood how one primer "corresponds" to another. The specification does not define this term, and therefore, the metes and bounds of the claim are unclear.

D) Claims 16 and 18 recite the limitation "the amplified DNA" in line 2 of each claim. There is insufficient antecedent basis for this limitation in the claim, that is, the term "amplified DNA" does not appear in independent claim 14.

E) Claim 17 contains the trademark/trade name PicoGreen™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a DNA intercalating agent and, accordingly, the identification/description is indefinite.

F) Claims 17 and 18 recite the limitation "the detection reagent" in lines 1 and 3 respectively. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Atlas et al. (US Patent 5,298,392; 3/29/1994).

The claim is drawn to a method of detecting bacteria in a liquid or liquefied sample by PCR comprising providing a liquid or liquefied sample, recovering bacteria from a liquid or liquefied sample, lysing the bacteria, performing PCR using a primer pair for amplifying a target gene, and detecting the presence of amplified DNA as an indication of the presence of bacteria carrying the target gene, wherein the target gene is the lamB gene from *E. coli*. Atlas teaches a process for detecting water-borne pathogens, particularly bacteria primarily of fecal origin, in water samples. The method taught by Atlas comprises 1) treating a water test sample in such a way that substantially all the water-borne pathogens and indicator microorganism are recovered and concentrated providing a liquid or liquefied sample and recovering bacteria from the liquid or liquefied sample), 2) treating the concentrated test sample to lyse cells and recover

substantially undegraded targeted DNA (lysing the bacteria to provide a DNA sample), 3) choosing a target gene and target DNA nucleotide sequence from the gene and incubating the target DNA nucleotide sequence of the test sample under amplification conditions wherein selected primers hybridize to separated target strands and a polymerase extends the primers (incubating the DNA sample under amplification conditions with a DNA polymerase and a primer pair for amplifying the target DNA sequence, and 4) detecting amplified target DNA sequence to determine the presence or absence of the pathogen or indicator organism in the test sample (detecting the presence of amplified DNA as an indication of the presence of bacteria carrying the selected target DNA sequence (see abstract, cols. 3 and 4 "summary of the invention"). Atlas specifically teaches that target genes for particular water borne human pathogens include lamB for *Escherichia*, *Salmonella*, and *Shigella* species (col. 4, lines 42-47) and also specifically teaches a method as outlined above using primers directed to the lamB gene of *E. coli* to detect *E. coli* (col. 12 "recovery of coliform DNA", col. 13 "PCR amplification and Targeted DNA Coliform Sequences, col. 14, "Detection of Amplified Targeted Coliform DNA sequences). Atlas teaches specific primer sequences for use in the method (col. 13, lines 42-57).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 6-8, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atlas et al. (US Patent 5,298,392; 3/29/1994) in view of Clement et al (Cell, vol. 27, pp 507-514, Dec. 1981).

Atlas teaches a process for detecting water-borne pathogens, particularly bacteria primarily of fecal origin, in water samples. The method taught by Atlas comprises 1) treating a water test sample in such a way that substantially all the water-borne pathogens and indicator microorganism are recovered and concentrated providing a liquid or liquefied sample and recovering bacteria from the liquid or liquefied sample), 2) treating the concentrated test sample to lyse cells and recover substantially undegraded targeted DNA (lysing the bacteria to provide a DNA sample), 3) choosing a target gene and target DNA nucleotide sequence from the gene and incubating the target DNA nucleotide sequence of the test sample under amplification conditions wherein selected primers hybridize to separated target strands and a polymerase extends the primers (incubating the DNA sample under amplification conditions with a DNA polymerase and a primer pair for amplifying the target DNA sequence, and 4) detecting amplified target DNA sequence to determining the presence or absence of the pathogen or indicator organism in the test sample (detecting the presence of amplified DNA as an indication of the presence of bacteria carrying the selected target DNA sequence (see abstract, col. 3 and 4 "summary of the invention"). Atlas specifically teaches that target genes for particular water borne human

pathogens include lamB for Escherichia, Salmonella, and Shigella species (col. 4, lines 42-47) and also specifically teaches a method as outlined above using primers directed to the lamB gene of E. coli to detect E. coli (col. 12 "recovery of coliform DNA", col. 13 "PCR amplification and Targeted DNA Coliform Sequences, col. 14, "Detection of Amplified Targeted Coliform DNA sequences). Atlas teaches specific primer sequences for use in the method (col. 13, lines 42-57).

It is noted that Atlas does not teach the specific primer sequences (claims 1-3, and 6-7) of the instantly claimed invention, however, Atlas does teach that different primer pairs to the lamB gene region (including the coding sequence) were capable of detecting *E. coli* in water samples. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made primers for amplification and detection of regions of lamB from *E. coli* for the purpose of detecting *E. coli* having the sequences of the SEQ ID NOS in the claims from the teaching of Atlas in order to make the claimed invention as a whole because Atlas teaches that different primer pairs to the lamB gene region (including the coding sequence) were capable of detecting *E. coli* in water samples. The ordinary artisan would have been able to construct primers to the lamB coding sequence as the sequence was known in the art at the time of the invention and taught by Clement et al (Fig 1). SEQ ID NO: 1 is identical to positions 902-925 in Fig. 1, SEQ ID NO: 2 is identical to positions 903-925 in Fig 1, SEQ ID NO: 3 is identical to 902-924 in Fig. 1, SEQ ID NO: 14 is complementary to positions 1058-1081 in Fig. 1, SEQ ID NO: 15 is complementary to positions 1058-1080 in Fig. 1, and SEQ ID NO: 16 is complementary to positions 1059-1081 in Fig. 1. The ordinary artisan would have been

motivated from the teachings of Atlas to have used regions in the coding sequence of lamB. The primers that could be generated from this coding region would have been considered functionally equivalent because there is nothing apparent from the sequence that would have made one region superior to another in a method of detecting *E. coli*. The specific SEQ ID NOS in the claims fall with the genus of these obvious functional equivalents in the absence of evidence to the contrary. With regard to the specific primer pair of claim 7, it is noted that the specification teaches that this specific primer combination did not detect a number of other bacterial genus and species, however Atlas teaches that different levels of specificity were achieved with specific primer pairs depending on the temperature of the primer annealing step during the PCR (col. 17, line 33). As the claim is not limited to specific PCR conditions and to detecting *E. coli* specifically while not detecting other bacteria, Atlas provides a reasonable expectation of success that different primer pairs directed to the lamB gene of *E. coli* would be functional in a method of detecting *E. coli* in a water sample.

With regard to the limitation in claim 8 which specifies that "the presence of *E.coli* is indicated when a signal is obtained which exceed a predetermined threshold", Atlas teaches that detection of *E. coli* target lamB gene is brought about using gel electrophoresis or radiolabeled gene probes (see col. 14, lines 40-42). Atlas teaches that either the amplified target DNA references were separated on gels, stained in ethidium bromide solution, and visualized with a Photo/PrepI UV transilluminator, or that probes labeled with ^{32}P were used to detect the amplified target DNA (col. 14, lines 55-col. 15, line 15). Therefore, it would have been *prima*

facie obvious to one of ordinary skill in the art at the time the invention was made to have detected the amplified target DNA with either the intercalating agent ethidium bromide or radiolabeled probes as Atlas teaches the successful detection of lamB from *E. Coli* using such methods. The teachings of Atlas would have provided the ordinary artisan with the motivation to detect the amplified target DNA with an intercalating agent or with radiolabeled probes and would also have provided a reasonable expectation of success that such methods would effectively detect the target DNA. The claims have been broadly interpreted to encompass the ethidium bromide staining method or the ^{32}P labeled DNA probe detection methods taught by Atlas, as both methods encompass measuring a signal (indication of the presence of target DNA) above a specific background threshold.

With regard to claims 14 - 16, Atlas teaches and claims kits containing the primers and detection probes (detection agent) of the invention of Atlas (see col. 3, lines 2-24, and claims 15-27). Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package primers of the instantly claimed invention in kit format for use in a detection method as Atlas teaches doing so. The ordinary artisan would have been motivated to provide primers in kit format for the purposes of providing pre-weighed, premeasured reagents to reduce sample handling and experimental error.

10. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Atlas in view of Clement as applied to claims 1-3, 6-8, and 14-15 above, and further in view of Molecular Probes

Catalog (6th edition, 1996, pp 161-162; Handbook of Fluorescent Probes and Research Chemicals).

The teachings of Atlas are provided in section 9 above. Although the kit taught by Atlas does not include the detection reagent PicoGreen ™ (claim 17), Atlas does teach kits which include detection probes and Atlas teaches that two different detection methods are effective in detecting target DNA, they include staining with the intercalating agent ethidium bromide, and radiolabeled probes. Molecular Probes teaches an improved reagent, PicoGreen, which provides exceptional sensitivity for detecting double stranded DNA in solution (p. 162, col. 1, "PicoGreen dsDNA Quantitation reagent. Molecular Probes teaches that it is possible to quantitate PCR products from low-cycle number or low-target number reactions (p. 162, col. 1, lines 11-12). Molecular Probes teaches that with the PicoGreen reagent, it is possible to reliably detect as little as 25pg/ml of dsDNA using fluorescein excitation and emission wavelengths and a standard fluorimeter or 250pg/ml using a fluorescent microplate reader (p. 162, col. 1, "Sensitivity"). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have improved the kits for detecting target DNA taught by Atlas by including PicoGreen as a detection agent as Molecular Probes teaches of the improved sensitivity of detecting dsDNA in solution (amplified DNA taught by Atlas is in solution) using PicoGreen. The ordinary artisan would have been motivated to include the PicoGreen reagent in kit format for the purposes of improving the kits taught by Atlas.

11. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atlas in view of Clement as applied to claims 1-3, 6-8, and 14-15 above, further in view of Challberg et al (WO 93/10623, May 27, 1993), and further in view of Biosystems Reporter (vol. II, 1996, pages 1-3).

It is noted that the kits taught by Atlas do not include a detection well having streptavidin coated thereon wherein the amplified DNA sequence is detected by the detection reagent (claim 18) and wherein one of the first primer and second primer is biotinylated (claim 19).

Challberg et al teaches a non radioactive hybridization method and kit for the detection of genetic defects, microbial infections or viral infections. Challberg teaches a method for the detection of target nucleic acids of interest wherein primers for amplification of the nucleic acid are biotinylated and detection of amplification reaction products occurs by hybridization with an unlabeled probe and upon hybridization of amplified nucleic acid with detection probes, the hybrids are bound to a solid phase coated with streptavidin (p. 9, lines 24-36) and detected, for example with an antibody (Challberg teaches that preferably, streptavidin coated microtiter plates are used, p. 12, lines 36-37). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have improved the kits taught by Atlas, with biotinylated primers and streptaviden coated wells as taught by Challberg for use with the detection method of Challberg for the purposes of providing a safer, nonradioactive detection method. Further, the ordinary artisan would have been motivated to improve the kits of Atlas with the teachings of Challberg as the use of streptavidin coated wells, for example in microtiter

plates, would have been an improvement over the kits of Atlas as such components can be incorporated into an automated system and provide for more rapid detection. For example, Biosystems Reporter teaches an automated PCR based system for the detection of *Salmonella* in Food using a 96 microwell tray wherein PCR reactions to amplify *Salmonella* DNA are conducted in the wells and detection with fluorogenic probes occurs within the wells. Biosystems Reporter teaches that this offers the ability to directly detect the organism within 24 hours using an easy, specific, and gel free method that provides reliable results.

Conclusion

12. No claims are allowable over the cited prior art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
Jehanne Souaya
March 15, 2002

Application No.: 09/634,960

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☑ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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